Chronic Beryllium Disease: Diagnosis and Management

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Chronic beryllium disease is predominantly a pulmonary granulomatosis that was originally described in 1946. Symptoms usually include dyspnea and cough. Fever, anorexia, and weight loss are common. Skin lesions are the most common extrathoracic manifestation. Granulomatous hepatitis, hypercalcemia, and kidney stones can also occur. Radiographic and physiologic abnormalities are similar to those in sarcoidosis. While traditionally the pathologic changes included granulomas and cellular interstitial changes, the hallmark of the disease today is the well-formed granuloma. Immunologic studies have demonstrated a cell-mediated response to beryllium that is due to an accumulation of $CD4^+$ T cells at the site of disease activity. Diagnosis depends on the demonstration of pathologic changes (i.e., granuloma) and evidence that the granuloma was caused by a hypersensitivity to beryllium (i.e., positive lung proliferative response to beryllium). Using these criteria, the diagnosis of chronic beryllium disease can now be made before the onset of clinical symptoms. Whether, with early diagnosis, the natural course of this condition will be the same as when it was traditionally diagnosed is not known. Currently, corticosteroids are used to treat patients with significant symptoms or evidence of progressive disease. — Environ Health Perspect 104(Suppl 5):945–947 (1996)

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Chronic beryllium disease (CBD), first described in 1946, is a disease of the 20th century. Hardy and Tabershaw described 17 cases in the fluorescent lamp industry, in which symptoms developed 6 months after initial exposure to beryllium (*1*). Many patients had far advanced disease as evidenced by their severe symptoms. Anorexia was present in all 17, 16 had weight loss, 15 had dyspnea on exertion, and 13 complained of cough. On physical examination, rales were present in 13, tachycardia in 10, fever in 9, cyanosis in 5, edema in 5, and clubbing in 2. As expected for the initial description of a syndrome, patients were identified only if severe disease was present. The delayed onset and persistent nature of this condition were contrasted to a previously described complication of beryllium exposure, acute beryllium disease (*2*). Acute beryllium disease was only seen after intense exposure to beryllium and was thought to be an acute chemical burn. This latter condition is largely of historical interest and would occur today only if there were a plant explosion.

To collect all possible cases of beryllium disease, a case registry was developed. Six criteria were developed for entering cases into the registry, two based on documenting exposure and four based on evidence of a chronic pulmonary process. For an individual to be entered into the beryllium registry, four of the six criteria had to be satisfied and the patient had to have a history of exposure or elevated tissue levels of beryllium. Workers at risk for beryllium exposure were production and maintenance workers in beryllium extraction; basic beryllium plants producing metallic beryllium, beryllium alloys, or beryllium oxide powder; foundries melting beryllium alloys; beryllium machine shops; and plants processing beryllium oxide powder. Operations that put workers at risk included grinding, lapping, or abrading beryllium-containing materials; welding, brazing, or melting such materials; BeO-furnace cleaning or rebuilding; laser cutting, scribing, or trimming; dental laboratory operations; BeO extrusion or pressing; heat treatment of beryllium alloys; and chemical milling of beryllium. Evidence of a chronic pulmonary disease was based on clinical symptoms, chest radiographs, pulmonary function tests, or pathology.

The clinical symptoms usually reflect a chronic pulmonary disease process (*3*). Thus, cough and shortness of breath are usually present. However, nonspecific symptoms such as fever, anorexia, and weight loss may also be present. In addition, granulomatous skin lesions may be seen in some patients. Hypercalcemia and kidney stones also have been reported. While granulomatous hepatitis has been described, it is rarely symptomatic. Radiologic abnormalities are usually similar to those observed in sarcoidosis (*4*). These include fibronodular changes that usually involve the upper lobe. Hilar and mediastinal adenopathy are present in about 50% of patients but frequently the nodes are small. Large, potato-sized nodes that can be seen in sarcoidosis have not been described in chronic beryllium disease. Thin-section computed tomographic features of chronic beryllium disease have been compared to chest radiographs (*5*). While abnormalities were detected in 10 of 13 patients with normal chest radiographs and biopsy-proven disease, the abnormalities detected—parenchymal nodules and septal lines—are not specific for chronic beryllium disease.

The typical pulmonary function abnormalities observed in chronic beryllium disease are those that have been associated with other interstitial lung disorders. These include a decrease in the vital capacity and the total lung capacity (i.e., a restrictive pattern) and a reduction in the diffusing capacity (*6*). While obstructive changes also have been observed, these changes tend to occur late in the disease (*7*).

The classic pathologic changes that have been described in CBD were described in a review of 130 cases from the beryllium case registry (*8*). The majority (80%) of the patients had evidence of marked cellular interstitial changes. Over half of these patients had poorly formed or no granuloma formation. The remaining patients who had marked cellular interstitial changes had prominent and well-developed granuloma formation. Twenty percent of patients had little evidence of cellular interstitial changes but did have numerous and

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Abbreviations used: CBD, chronic beryllium disease; BeO, beryllium oxide; BAL, bronchoalveolar lavage; DL_{CO}, diffusing capacity for carbon monoxide.

well-formed granulomas. In contrast to this study, most patients who appear to have been diagnosed in the 1980s showed evidence of granuloma formation (*6,9,10*). The difference between this earlier study and current studies may be the lower environmental exposure that has occurred in industry in the last 20 years. Today, the well-developed granuloma is considered the classic pathologic change in CBD. These granulomas are indistinguishable from those present in sarcoidosis. While beryllium can be detected within granulomas by specialized techniques, these techniques are not readily available (*11*).

As the role of immunologic mechanisms in CBD have become clearer, immunologic tests of beryllium hypersensitivity have played an increasing role in diagnosis of the disease (*12*). Initially, beryllium hypersensitivity was determined by patch testing (*13*). However, because of fears of sensitization and untoward reactions, testing of beryllium hypersensitivity did not become practical until the 1970s when *in vitro* blood lymphocyte proliferation tests were developed (*14,15*). These tests were used to confirm a history of beryllium exposure and sometimes (mistakenly) used to exclude a diagnosis of beryllium disease. In the 1980s, lymphocyte proliferation testing was applied to cells obtained by bronchoalveolar lavage (BAL) (*6,9,10,16–19*). These tests confirmed not only the ability of beryllium to stimulate a cell-mediated hypersensitivity reaction, but also the accumulation of beryllium-sensitive $CD4^+$ T lymphocytes (*6,18*) at the site of disease activity.

Based on these and other studies, the pathogenesis of CBD is thought to involve the following processes: First, airborne beryllium is inhaled and deposited in the airspaces in the lung. Because beryllium is poorly excreted from the lungs, this beryllium will persist for a prolonged period (*20*). After an unknown period, certain individuals will become sensitive to beryllium. Beryllium, acting as a hapten, binds proteins/peptides in the lung and elicits a proliferation of $CD4^+$ T lymphocytes (*6,18*). These sensitized lymphocytes secrete a variety of cytokines that are responsible for the recruitment, activation, and maturation of macrophages into epithelioid cells. Epithelioid cell granulomas form and lead to fibrosis and destruction of normal lung parenchyma.

Based on these immunologic findings, a new gold standard for the diagnosis of CBD was proposed (*21*), based on pathologic evidence of granulomatous disease and beryllium hypersensitivity of bronchoalveolar cells. The gold standard included histologic evidence of granuloma, immunologic evidence that granuloma was caused by beryllium hypersensitivity, and a positive proliferative response of bronchoalveolar cells to beryllium. Other criteria, though not considered a gold standard, were strongly suggestive. These involved studies consistent with pulmonary granulomas, including radiologic (upper lobe nodular densities ± adenopathy) and physiologic (restrictive process or abnormal DL_{CO}) studies. Equally suggestive studies consistent with beryllium hypersensitivity or exposure were those involving positive blood proliferative response to beryllium and localization of beryllium within the granuloma. Using these new criteria, a specific diagnosis of chronic beryllium disease could be determined. There are several important implications to the use of these new criteria. First, a history of beryllium exposure is not required to make a diagnosis of chronic beryllium disease. Since there have not been any descriptions of individuals who have bronchoalveolar lymphocytes that react to beryllium and do not have a history of exposure to beryllium, the implication is that if an individual has bronchoalveolar lymphocytes that respond to it, that individual must have had some exposure to beryllium. The challenge, then, is to determine how the exposure occurred. The second implication of these gold-standard criteria is that a patient need not have clinical symptoms, radiographic abnormalities, or abnormalities on pulmonary function testing to be diagnosed with CBD. Thus, the diagnosis can be made earlier than was previously possible. Whether, with early diagnosis, the natural course of this condition will be the same as when it was traditionally diagnosed is not known. Finally, the use of the proliferation test as part of the diagnostic criteria for CBD suggests that blood proliferation testing for beryllium hypersensitivity might be a useful means for early detection. Large-scale studies are currently in progress since initial surveys (*9,10*) indicated that screening workers with a blood proliferation test will identify those with early disease that would not have been detected otherwise.

In contrast to most occupationally related lung disease, the early detection of chronic beryllium disease is useful since treatment of this condition can lead not only to regression of the signs and symptoms, but also should prevent further progression of the disease. The management of CBD is based on the hypothesis that suppression of the hypersensitivity reaction (i.e., granulomatous process) will prevent the development of fibrosis. However, once fibrosis has developed, therapy cannot reverse the damage. There have been no controlled studies to determine the optimal treatment for this condition. We currently follow patients with yearly history and physical examinations, chest radiographs, pulmonary function tests, and exercise physiology until there is definite evidence that the beryllium hypersensitivity is beginning to cause damage. Patients with evidence of early lung damage are treated with 40 mg of prednisone on alternate days for 6 months. Prednisone is tapered by no more than 10 mg every other month until there is evidence of renewed disease activity. Disease activity is monitored by the same tests that demonstrated deterioration. The lowest dose of prednisone that prevents disease is maintained. Whether individuals require a lifetime of treatment remains uncertain. However, animal studies (*20*) suggest that once beryllium is deposited in the lungs, the clearance is very slow. Thus, with a persistent stimulus, it is likely that prolonged corticosteroid therapy will be needed.

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